REMARKS

Reconsideration is requested.

Claims 23-32 have been cancelled, without prejudice. Claims 33-45 are pending. No new matter has been added.

The objection to claim 24 noted on page 2 of the Office Action dated December 31, 2002 (Paper No. 19) is moot in view of the above.

The Section 112, second paragraph, rejection of claims 23-32 is moot in view of the above. The claims are submitted to be definite. The Examiner is requested to consider the following in this regard:

Independent claims 33 and 35 recite "a mutant herpes simplex virus consisting essentially of a non-functional gamma 34.5 gene." Replacement of "comprising..." with "consisting essentially of..." has the result of excluding ingredients which would affect the basic and novel characteristics of the mutant herpes simplex virus defined in the claim such that the only non-functional gene within the claim scope is the non-functional gamma 34.5 gene.

Independent claims 34 and 36 indicate that the mutation in the mutant herpes simplex virus consists essentially of a non-functional γ34.5 gene, also excluding ingredients which would affect the basic and novel characteristics of the mutant herpes simplex virus defined in the claim.

The applicants submit that the pending claims are definite.

The § 102 rejection of claims 23-30 over Martuza (U.S. Patent No. 6,139,834) is moot in view of the above. The § 102 rejection of claims 23-26 and 28-30 over

Roizman (U.S. Patent No. 6,340,673) is moot in view of the above. The §103 rejection of claims 23 and 29-32 over the combination of Martuza, MacLean (Journal of General Virology 72:631-639, 1991) or Brown (WO 92/13943), and Markert (Neurosurgery 32:597-603, 1993) is moot in view of the above. The §103 rejection of claims 23, 27 and 29-32 over Roizman in view of Martuza and either MacLean or Brown is moot in view of the above. The pending claims are submitted to be patentable over the Examiner's citation of the art and consideration of the following in this regard is requested.

The applicants submit that Martuza et al. (US 6,139,834) specifically relates to a mutant herpes simplex virus-1 for killing nervous system tumour cells (column 1 lines 16-22). The Examiner relies on column 3 line 61-67 and column 11 lines 45-55 to support the contention that Martuza is not limited to treatment of neuronal tumours. Whilst objects of the invention of Martuza incorporate tumour cell kill of non-nervous tissue origin (column 3 lines 26-28) there is no support in Martuza, by way of specific examples, of successful treatment of non-neuronal tumour cells in mammals, nor is there any indication of a reasonable expectation to achieve such a treatment. All of the specific examples described in Martuza relate to treatment of neuronal tumour cells and the alleged object of killing non-neuronal tumour cells is not met by the disclosure.

In this regard, Martuza discusses potential cell specific targeting of herpes simplex virus mutants (column 10 lines 28-45). This is a speculative application of the disclosure of Martuza which, if successful, teaches the requirement to adapt herpes simplex virus mutants for non-neuronal targeting by placing a viral replication gene under direct control of a cell specific promoter. The inevitable result of this approach

would require the cell specific promoter as an essential feature of the herpes simplex virus mutant. This would result in a herpes simplex virus mutant consisting essentially of a non-functional γ34.5 gene and cell specific promoter positioned to control the selected viral replication gene as essential elements hence not being within the currently claimed scope of the present invention.

Applicants submit that modification of the ribonucleotide reductase (RR) gene is an essential feature of Martuza. The Examiner submits that herpes simplex virus mutants deficient in only the γ34.5 genes such as R3616 are already attenuated for neurovirulence due to an inability to replicate in the CNS. Mutants such as R3616 are part of the state of the art, and this must be considered to appreciate the essential nature of ribonucleotide reductase modification in Martuza.

Considering the general state of the art, Roizman (US 6,340,673) defines neuronal avirulence due to inability of mutant viruses to replicate in the CNS wherein infection of neuronal cells with such mutants incapable of expressing the γ34.5 gene results in shut off of cellular protein synthesis i.e. neuronal avirulence due to latency of γ34.5 mutants, wherein replication and lysis is inducible in neuronal tumour cells (see in particular Roizman column 18 lines 4-15). Roizman also indicates at column 18 lines 13-15 that infection of non-neuronal cells with wild-type or mutant viruses results in a sustained protein synthesis and production of infectious progeny i.e. indicative of a replication and lysis rather than latency. As a result, the state of the art is indicative that herpes simplex virus mutants comprising non-functional γ34.5 gene cannot selectively target non-neuronal tumour cells as there is no differentiation in replication and lysis between non-neuronal somatic and non-neuronal tumour cells. This is relevant to the

teaching of Martuza in that the state of the art teaches that herpes simplex virus mutants having non-functional γ34.5 gene will not selectively kill tumour cells of non-neuronal origin as the attenuated neurovirulence of herpes simplex virus mutants deficient in only the γ34.5 gene, e.g. R3616 as cited by the examiner at column 6 lines 49-66 of Martuza is considered in the prior art not to result in avirulence in non-neuronal cells.

Accordingly, the expectation in Martuza is that herpes simplex virus mutants deficient in only γ34.5 gene, whilst attenuated for neurovirulence are not attenuated for virulence in non-neuronal cells and that incorporation of a modification to ribonucleotide reductase gene is essential for operation of selected virulence in non-neuronal tumour cells which is an essential feature for the killing of non-neuronal tumour cells in Martuza. This leads to the inevitable result that modification of ribonucleotide reductase gene is considered in Martuza to be an essential feature for killing non-neuronal tumour cells as in the absence of modification to ribonucleotide reductase Martuza teaches an absence of selection of cell kill between non-neuronal somatic cell and non-neuronal tumour cells.

Roizman (US 6,340,673) specifically teaches methods of treatment of neuronal cells (column 6 line 15-17). The passage at column 5 line 62-64 is a vague indication of a possible use of herpes simplex virus mutants containing non-functional γ34.5 gene to treat tumorogenic disease in non CNS regions of the body. However, Roizman as a whole provides no specific teaching of treatment of non-neuronal cancer with such herpes simplex virus mutants and such statements are simply speculation. Moreover, Roizman indicates the disclosure to relate to use of herpes simplex virus γ34.5 gene

mutants as therapeutics for neuronal programmed cell death (see column 13 line 34-37).

The disclosure in Roizman at column 9 line 50-61 merely recites desirable speculative methods (see use of "envisions" at line 49) for treatment of cancer and reinforces the fact that Roizman does not specifically teach, by way of specific examples, use of herpes simplex virus mutants in treatment of non-neuronal tumours.

The disclosure in Roizman at column 18 lines 10-15 read in conjunction with column 17 line 52 to column 18 line 9 teach that whilst shut off of cellular protein synthesis occurs in cells of neuronal origin, consistent with attenuated neurovirulence of mutants such as R3616, infection of cells of non-neuronal origin with mutant viruses, or wild-type, results in sustained protein synthesis and production of infectious progeny. This indicates that Roizman considers that herpes simples virus mutants deficient in functional γ34.5 gene cannot be selectively targeted to non-neuronal cells as no avirulent phenotype is present in non-neuronal cells, necessary if infection in tumour cells is to result in induced replication and lysis, these features being essential to the mechanism of action in treatment of non-neuronal tumour cells.

Accordingly, Roizman does not teach successful use of herpes simplex virus mutants deficient in γ34.5 gene function which can selectively target non-neuronal tumour cells over non-neuronal somatic cells to provide an effective and functional treatment of non-neuronal cancer.

The pending claims are drawn to a method of treating non-neuronal cancer using mutant herpes simplex virus consisting essentially of a non-functioning gene which is the γ34.5 gene. The claimed invention does not include the presence of a non-

functional ribonucleotide reductase gene which is essential to Martuza for the killing of tumour cells as Martuza builds on the prior art contention that non-neuronal tumour cell specific kill cannot be achieved without inclusion of a modification to the herpes simplex virus genome such that replication and lysis is only initiated on infection of tumour cells. Hence, modification of ribonucleotide reductase in Martuza is essential according to the teaching of Martuza for killing non- neuronal tumour cells. The presently clamed invention is submitted to be novel over Martuza in that, at a minimum, the presently claimed invention does not include modification of the ribonucleotide reductase gene.

As Roizman does not teach any specific examples of treatment of non-neuronal cancer with herpes simplex virus mutants containing non-functional γ34.5 gene, but rather, at best, only speculative statements as to its potential uses, there is no disclosure in Roizman which anticipates the presently claimed invention. In particular, Roizman emphasizes the lack of attenuated virulence of mutant herpes simplex virus in non-neuronal cells (column 18 lines 10-15) with the result that non-neuronal tumour specific cell kill is not perceived as being achievable using the teaching of Roizman. As Roizman does not teach any mode of successfully treating non-neuronal cancer with mutant herpes simplex virus having only a non-functional γ34.5 gene, the presently claimed invention is submitted to be patentable over Roizman.

As for the Examiner's cited combination of art, the Examiner is requested to consider the following.

Martuza teaches modification of ribonucleotide reductase as being essential, as noted above. As such, the ordinarily skilled person was directed to consider such a modification to ribonucleotide reductase being essential to any further modifications of

Martuza such that the ordinarily skilled person was led away from the presently claimed invention. Combining the teachings of the remaining cited prior art would have always required the inclusion of a modification to ribonucleotide reductase and hence the product of such combinations would not have led to the presently claimed invention.

As discussed above, Roizman teaches no expectation of success in treatment of non-neuronal cancer, no specific examples of the speculative applications of herpes simplex virus mutants containing non-functional γ34.5 gene being disclosed. In particular, Roizman directed the ordinarily skilled person to the conclusion that a non-neuronal cell avirulence phenotype necessary for inducement of tumour cell specific kill in non-neuronal cancer is not characteristic of herpes simplex virus mutants containing non-functional γ34.5 genes.

There is no teaching in Brown (WO 92/13943), Markert or MacLean which would have directed the ordinarily skilled person to consider an expectation of success in treatment of non-neuronal cancer with herpes simplex virus mutant containing non-functional γ34.5 gene.

The cited art either taught the ordinarily skilled person that inclusion of a modified ribonucleotide reductase was an essential element of any method of treatment of non-neuronal cancer using mutant herpes simplex virus or that there was no expectation of success of using mutant herpes simplex virus having non-functional γ34.5 gene without modification to ribonucleotide reductase due to the lack of avirulent characteristics in non-neuronal cells.

Accordingly, the findings of the present invention are surprising given the cited art and the claims are correspondingly patentable over the same.

The claims are submitted to be in condition for allowance and the notice to that affect is requested.

Respectfully submitted,

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